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Intracerebral Periventricular Pseudocysts in a Fetus with Mitochondrial Depletion Syndrome: An Association or Coincidence

M. Rohrbach^a D. Chitayat^{a,d} G. Maegawa^a S. Shanske^g G. Davidzon^g
K. Chong^{a,d} J.T.R. Clarke^a A. Toi^e M. Tarnopolsky^f B. Robinson^b S. Blaser^c

^aDivisions of Clinical and Metabolic Genetics, Department of Pediatrics, ^bDepartment of Biochemistry and Paediatrics and ^cDiagnostic Imaging and Neuroradiology, The Hospital for Sick Children, ^dThe Prenatal Diagnosis and Medical Genetics Program, Department of Obstetrics and Gynecology, ^eDepartment of Diagnostic Imaging, Mount Sinai Hospital, University of Toronto, Toronto, Ont., ^fNeuromuscular and Neurometabolic Unit, McMaster University Medical Center, Hamilton, Ont., Canada; ^gDepartment of Neurology, Columbia University College of Physicians and Surgeons, New York, N.Y., USA

Key Words

Mitochondrial depletion • Prenatal ultrasound • Fetal magnetic resonance imaging • Brain pseudocyst

Abstract

We report the prenatal ultrasound and magnetic resonance imaging finding of periventricular, large subependymal pseudocysts (SEPCs) in a patient who was later diagnosed as having mitochondrial depletion syndrome (MDS). To our knowledge, this is the first report of fetal SEPCs in a patient with MDS. These findings may provide an important diagnostic tool for prenatal diagnosis of MDS in at risk pregnancies when the gene mutation causing the condition has not been delineated. It may also direct the neonatologist in the postnatal care of the newborn detected prenatally with SEPCs in view of the association of this finding with infection, chromosome abnormalities, metabolic disorders and other abnormalities, when such findings are identified serendipitously. Further research is needed to find if the SEPCs detected in our patient is an association or a coincidental finding.

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Introduction

Mitochondrial DNA (mtDNA) depletion syndrome (MDS) is a clinically heterogeneous group of disorders, defined as having quantitative reduction in mtDNA copy number [1]. The size and sequence of the mtDNA are generally normal. Reduction in mtDNA quantity leads to insufficient synthesis of respiratory chain complexes I, III, IV and V [1–4]. The human mitochondrial electron transport chain consists of five enzymatic complexes, ubiquinone and cytochrome c. The main function is to transfer electrons through intramolecular redox centers of complexes I through IV, with the production of ATP by the fifth enzymatic complex. Except for complex II, which is encoded entirely by nuclear genes, all respiratory chain complexes are encoded, at least in part, by mtDNA, which encodes a total of 13 proteins, all of whom are present in respiratory chain complex I, III, IV and V. Nuclear-encoded proteins/enzymes are required for both enzymatic complexes and for replication and maintenance of mtDNA.

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Dr. D. Chitayat, The Prenatal Diagnosis and Medical Genetics Program
Department of Obstetrics and Gynecology, Mount Sinai Hospital
700 University Avenue, 3rd Floor, Room 3292
Toronto, Ont. M5G 1Z5 (Canada)
Tel. +1 416 586 45 23, Fax +1 416 586 47 23, E-Mail dchitayat@mtsina.on.ca

Table 1. Comparison between the clinical and laboratory manifestations of MDS and methylmalonic acidemia

	Case 1 [40]	Case 2 [40]	Present case
Urine organic acids analysis	Methylmalonic acid	Methylmalonic acid	Methylmalonic acid
Organic acids found elevated	3-hydroxypropionic 3-hydroxyvaleric Methylmalonic 3-methylglutaconic 2-oxoglutaric acid	3-hydroxypropionic 3-hydroxyvaleric Methylmalonic 3-methylglutaconic 2-oxoglutaric acid	3-hydroxypropionic 3-hydroxyvaleric Dicarboxylic acid 3-hydroxybutyric
Plasma acylcarnitines	–	–	propionylcarnitine methylmalonylcarnitine
Plasma amino acids	normal	normal	normal
Onset of lactic acidosis	5th month of life	11th month of life	2nd day of life
Ophthalmological exam	bilateral papillary edema	–	normal
Brain imaging, MRI/CT	frontal lobe atrophy normal myelination	diffuse cortical atrophy	bilateral periventricular pseudocysts and normal myelination
Course	death at 3 years of age	death at 3 years of age	death at 7 days of life
Ethnic background	Hispanic	Hispanic	Chinese

Mutations in 5 nuclear genes have been identified thus far in patients with MDS [5]. The disease may affect multiple or single organs, e.g. liver and/or muscle and brain and/or heart and kidney, with onset of symptoms usually in the first year of life. Most affected patients die in early childhood [4–6] (table 1). Mutations in the thymidine kinase 2 gene (*TK2*), located on chromosome 16q22 [7–9], were found to be associated with a myopathic form of the syndrome, whereas mutations in the deoxyguanosine kinase gene (*DGUOK*) on chromosome 2p13 [10–18] and polymerase- γ gene (*POLG1*) [19–22] have been implicated in the hepatocerebral form. Thymidine phosphorylase (*TP*) defects were found in some cases with leukodystrophy and a gastrointestinal disorder [23], and most recently, mutations in the succinyl-coenzyme A synthase gene (*SUCLA2*) were identified in 4 infants with severe developmental delay, epilepsy, hearing loss, anemia and Leigh-like lesions on brain magnetic resonance imaging (MRI) [24]. In addition, adenine nucleotide translocator 1 (*ANT1*) and mitochondrial replicative helicase *Twinkle*, both affecting mtDNA stability, were found to be involved in some cases of mtDNA depletion [25]. Biochemical analyses of the affected tissues generally show low activity of all four mitochondrial respiratory chain complexes I, III, IV and V, and Southern blot analysis or quantitative polymerase chain reaction (PCR) characteristically reveals a severe reduction in the ratio of mtDNA to nuclear DNA.

We report the finding of periventricular cysts on fetal brain ultrasound and MRI in a patient who postnatally was found to have MDS with 90% depletion of mtDNA in muscle. Although this can be a coincidental finding, in view of previous publications of this finding in other metabolic disorders [26, 27], we hypothesize that this might be a true association which can help in the prenatal diagnosis of this condition in at risk pregnancy, when the gene mutation causing the condition is not known.

Case Report

A nonconsanguineous Chinese couple was referred for counseling regarding their previous pregnancy, which resulted in neonatal death, in China, of a son who died at 2 days of age of an unknown etiology. The mother was a 30-year-old G2P1L1 woman at 13 weeks and 5 days of gestation when seen by us. The pregnancy was uncomplicated initially, and an ultrasound examination at 11 weeks and 5 days showed a single intrauterine pregnancy with a nuchal translucency of 2.7 mm. First trimester screening was not done and maternal serum screening showed negative screening for open neural tube defect and Down syndrome (the α -fetoprotein was 1.69 multiples of median). The couple decided to have an amniocentesis in view of their past obstetrical history of early neonatal death; this was performed at 17 weeks of gestation and showed a normal male karyotype (46, XY). Fetal ultrasound performed at the same time revealed bilateral ventriculomegaly and right renal pyelectasis of 4.9 mm. The rest of the fetal anatomy appeared normal. Fetal echocardiography performed at 20 weeks of gestation showed normal intracardiac anatomy with balanced

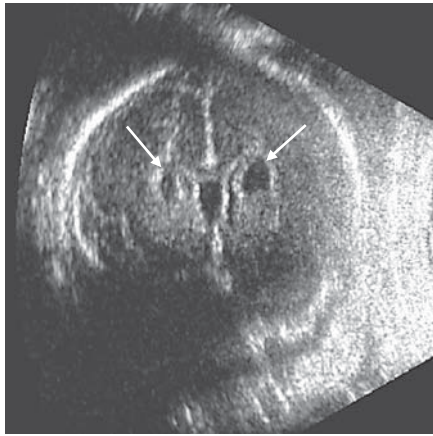


Fig. 1. Fetal ultrasound at 25 weeks' gestation showing bilateral subependymal cysts (arrows).

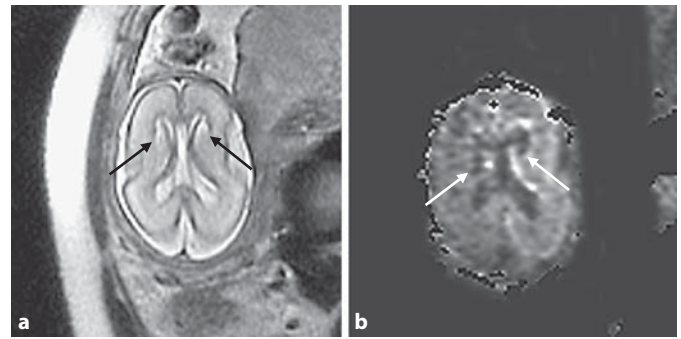


Fig. 2. Fetal MRI at 25 weeks' gestation showing bilateral periventricular cysts (arrows). **a** Fetal axial single-shot fast spin echo. **b** Diffusion-weighted imaging.

four-chamber view and normally related great vessels. Fetal ultrasound at 19 weeks' gestation showed a string of multilocular cystic spaces in the anterior subependymal caudothalamic region. Subsequent fetal ultrasound examination at 25 weeks of gestation demonstrated normal lateral ventricular size and normal renal ultrasound bilaterally; however, bilateral periventricular/subependymal cysts adjacent to the frontal horns were again seen (fig. 1). Fetal MRI confirmed the presence of the atypical cysts and noted that the remaining cerebral anatomy was normal (fig. 2). The cysts were extensive, paralleling the anterior horns and bodies of the lateral ventricles. Diffusion-weighted imaging and ADC maps demonstrated multifocal restriction in the brain substance adjacent to the cystic lesion. On follow-up ultrasound at 27 weeks of gestation, the cysts were located lateral to the caudate measuring 17×3 mm on the right and 14×7 mm on the left. At 33 weeks' gestation, the cysts increased in size to 16×6 mm on the right and 23×8 mm on the left side. Also, fetal weight estimates decreased from the 50th percentile to the 20th percentile. PCR for cytomegalovirus (CMV) done on the amniotic fluid sample obtained previously was negative and maternal screening for *Toxoplasma gondii*, other viruses (HIV, measles, and more), rubella, CMV, and herpes simplex (TORCH) analysis showed no evidence for an acute infection.

Delivery was induced at 37 weeks, because of intrauterine growth retardation (IUGR). The birth weight was 2,330 g (10–25th percentile) and the birth length was 46 cm (25th percentile). Apgar scores were 9 and 9 at 1 and 10 min, respectively. On the 2nd day of life, the infant developed persistent tachypnea and severe lactic acidosis (lactate 21.1 mM, pH 7.0, PCO_2 31 mm Hg, bicarbonate 8 mM and base excess of -8 mM) and a lactate to pyruvate ratio of 56.5 and the plasma CK values were normal. Initial urinary organic acids analysis was normal; however, analysis of subsequent samples revealed a high concentration of methylmalonic acid, as well as smaller amounts of methylcitrate and 3-hydroxypropionic acid. Analysis of the plasma acylcarnitines profile, run at the same time, showed the presence of propionylacylcarnitine and methylmalonylcarnitine (table 1). Septic workup

showed no evidence for an underlying infection as the cause for the persistent lactic acidosis. In addition, echocardiography confirmed normal cardiac anatomy. Brain MRI at day 6 of life confirmed the prenatal findings, with bilateral periventricular cysts and high lactate peak on magnetic resonance spectroscopy. Abnormalities previously seen on diffusion-weighted imaging had normalized.

The differential diagnosis at this point included methylmalonic aciduria (MMA), congenital lactic acidosis caused by defects in pyruvate carboxylase or pyruvate dehydrogenase, or a defect in the mitochondrial respiratory chain activity. Empiric therapy for pyruvate dehydrogenase and pyruvate carboxylase with thiamine and biotin, as well as with carnitine and vitamin B_{12} , and high-dose glucose infusion for MMA was started. Insulin was administered in an effort to maintain plasma glucose levels below 10 mmol/l as well as a continuous bicarbonate infusion to correct acidosis. In spite of this intensive treatment, the plasma lactate climbed to 23 mmol/l. He was started on dobutamine for cardiovascular support, but did not respond to these therapeutic measures and died at day 7 of life.

Methods

Muscle tissue was obtained on day 3 of life from quadriceps and examined by routine light and electron microscopy. The activities of citrate synthase and complexes I–V were determined in the mitochondria-enriched fraction of the quadriceps muscle, using standard polarographic and spectrophotometric methods [28]. Quantitative PCR analysis done on DNA isolated from muscle was performed as described [29]. Plasma acylcarnitine profiles were analyzed using tandem mass spectroscopy, and urine organic acids were quantified using gas chromatography-mass spectrometry. DNA analyses for *TK2*, *POLG*, and *SUCLA2* were performed as previously described [9]. *ANT1* and *Twinkle* mutation analysis was done as described by Naimi et al. [25].

Results

Biochemical analysis of muscle tissue showed NADH-cytochrome c reductase activity of $0.18 \mu\text{mol}/\text{min}/\text{g}$ (control 0.77 ± 0.12 ; normal range $0.5\text{--}1.9$), and NADH-cytochrome c reductase to citrate synthase activity ratio of 9.7% (normal $>10\%$), succinate cytochrome c reductase activity of $0.35 \mu\text{mol}/\text{min}/\text{g}$ (control 1.43 ± 0.46 ; normal range $0.57\text{--}2.3$), and succinate cytochrome c reductase to citrate synthase activity ratio of 13.8% (normal $>18\%$), cytochrome oxidase activity of $0.14 \mu\text{mol}/\text{min}/\text{g}$ (control 1.48 ± 0.57 ; normal range $0.58\text{--}2.5$), and cytochrome oxidase to citrate synthase activity ratio of 5.5% (normal $>11\%$), and citrate synthase activity was $2.52 \mu\text{mol}/\text{min}/\text{g}$ (control 3.35 ± 1.11 ; normal range $0.8\text{--}5.5$). Electron microscopy of muscle and skin demonstrated normal numbers of mitochondria and normal mitochondrial structure. There was no evidence of ragged red fibers on histochemical staining and no Cox negative fibers were observed. Quantitative PCR clearly demonstrated significant reduction (approximately 90%) of mtDNA when compared to nuclear DNA, as compared with controls. Mutation analysis of the genes *TK2*, *ANT1*, *POLG*, *SUCLA2* and mitochondrial replicative helicase *Twinkle* genes done by sequencing of the genes did not identify a mutation.

Discussion

Subependymal pseudocysts (SEPCs), also known as germinolytic cysts, are etiologically heterogeneous findings. They are called pseudocysts since they lack a membrane. They are probably the result of an injury to the periventricular subependymal germinal matrix mostly due to hemorrhage, infarction or intrauterine infection [30]. In a retrospective study by Shen and Huang [31], SEPCs were detected in 0.5–5.2% of neonates with 18/25 cases not known to be associated with a known perinatal insult. However, a more recent article by Heibel et al. [32] showed that the incidence is 0.35% (34/1,000) with 4/34 developing symptoms (hemiparesis and infantile spasm). In 2001, Makhoul et al. [33] reported 10 cases with SEPCs among the sick newborns admitted to the neonatal intensive care unit. Four of the 10 had CMV infection and 2 had other abnormalities. These authors also performed a meta-analysis of previously reported cases and concluded that if the pseudocysts are not associated with congenital abnormalities, IUGR, intrauterine infections or chromosome abnormalities, the prognosis is good. However,

these factors cannot be separated completely since infections, multiple abnormalities and chromosome abnormalities can also result in IUGR. The SEPC was also reported in association with two inborn errors of metabolism known to cause brain dysgenesis: Zellweger syndrome [26, 27] and holocarboxylase synthase deficiency [34], and our case adds to the increasing number of conditions associated with SEPCs, known to have poor prognosis. Thus, since SEPC is not a benign finding in many of the cases, and since it is prenatal in origin, its finding in a fetus should be thoroughly investigated to try and detect the etiology and thus the prognosis. To the best of our knowledge, our report is the first to document the findings of fetal ultrasound and MRI in a case with MDS as well as the first to show the finding of SEPC in this condition.

The patient reported by us presented with persistent, severe lactic acidosis and MMA on day 2 of life and had been shown to have cystic lesions in the anterior subependymal caudothalamic region of the brain on prenatal ultrasound and MRI starting as early as 19 weeks' gestation. Differential diagnosis initially included MMA based on the findings on acylcarnitine profiles in plasma. However, an increased lactate to pyruvate ratio in plasma suggested congenital lactic acidosis caused, for example, by a defect in the mitochondrial electron transfer chain, or by MDS, given the severe reduction in mtDNA in muscle tissue. Recently, it has been reported that defects in mitochondrial energy metabolism are often associated with elevated citric acid (TCA) cycle intermediates, in particular elevated urinary 3-methylglutaconic acid [35], dicarboxylic acids [36], or a combination of elevated dicarboxylic acids, 2-oxoglutarate, ethylmalonate and 3-methylglutaconate [37], elevated lactate, 3-hydroxybutyrate and acetoacetate [38], elevated 3-methylglutaconate and 3-methylglutarate [39]. Two unrelated cases of infantile MDS associated with MMA were reported [40]. Both patients had unremarkable pregnancies, but presented with lactic acidosis after a short symptom-free interval, as well as clinical features of muscle weakness, hypotonia and developmental delay. Muscle biopsy in each case demonstrated partial respiratory chain enzyme deficiency of cytochrome-oxidase with raised citrate synthase activity in one patient and decreased activities of multiple complexes in the other. The results of the analysis of the amount of mtDNA in the muscle tissue was in keeping with depletion of mtDNA, 24 and 39%, respectively, of the mean control value. Patient 2 died at the age of 3 years with severe metabolic acidosis and pneumonia. The mechanism of the increased excretion of methylmalonic acid and

related organic acids remained unknown. This report shares some clinical features with our case; however, the brain MRI and ophthalmological findings were different (table 1).

The finding of isolated SEPCs on fetal ultrasound as early as 19 weeks of gestation, as seen in our patient, and confirmed on prenatal and postnatal MRI, is the only prenatal imaging finding reported so far in association with MDS. MDS is a heterogeneous group of conditions affecting multiple or single organs. Clinically, it presents as a hepatocerebral form, a myopathic form, or a variant in which the dominant problem is cardiomyopathy. Variants of these conditions have been reported with differences in age at onset, organs involved, clinical course, and laboratory findings. Recently, mutations in *TK2*, *DGUK*, *POLG1*, *TP*, *ANT1* and *Twinkle* have been reported in association with MDS. The majority of patients with MDS show deficiencies in more than one respiratory chain complex, particularly complex I, II and IV. Complex II is usually spared since it is encoded solely by nuclear DNA. As in the case reported by Yano et al. [40], our patient had decreased activities of multiple complexes with respect to citrate synthase, including complex II, suggesting a secondary deficiency of nuclear-encoded enzymes. The observation of no Cox-negative fibers on the muscle cross-section might be related to the very young age of our patient at the time of muscle biopsy as most of the Cox-

negative fibers in MDS are found in older patients. The increased urinary secretion of methylmalonic acid is unclear, but the diagnosis of primary MMA was excluded. Methylmalonic peaks on gas chromatography cannot always be distinguished from peaks representing succinic acid, and accumulation of succinyl-CoA, one of the TCA cycle intermediates, would not be surprising in patients with mitochondrial energy defects.

The fact that we were unable to detect any mutations in any of the 5 genes known to be associated with MDS, and the clinical picture that was different from those previously found associated with other variants of MDS (table 1), suggests that our patient, along with the two recently published cases [40], might represent a novel disorder associated with this syndrome.

The pathophysiology of the cerebral pseudocysts found in the course of prenatal imaging is also unclear. However, it might be the result of prenatal lysis of undifferentiated germinal matrix [26, 31, 41], which could be the result of the metabolic insult. Further reports are required to determine if the finding of SEPC in our case is an association or a coincidence. If found to be an association, it can help in the prenatal diagnosis of the condition in at risk pregnancy, when no other tools for prenatal diagnosis, such as metabolic or DNA analysis, are available.

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